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EXAMINER	
WILSON, J	

ART UNIT	PAPER NUMBER
1803	

18N1/0601

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DATE MAILED: 06/01/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 10/04/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1 – 10 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1 – 10 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☒ been filed in parent application, serial no. 07/447,512; filed on 12/07/89.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 C.F.R. § 1.121(e).

The Abstract of the Disclosure is objected to because the abstract of the disclosure fails to provide an adequate description of the technical disclosure of the instant specification. The last term, "agent" in the abstract, should be plural to provide proper, grammatical verb and subject agreement. Correction is required. See M.P.E.P. § 608.01(b).

The reissue oath or declaration filed with this application is defective because it fails to particularly specify the errors relied upon, as required under 37 C.F.R. § 1.175(a)(3) and the reissue oath or declaration filed with this application is defective because it fails to particularly specify how the errors relied upon arose or occurred, as required under 37 C.F.R. § 1.175(a)(5).

It is noted that the reissue declaration fails specify the error in the specification. Applicants do not specifically delineate where in the specification the error occurs (e.g. where in the specification the ambiguous claim language is specifically found). Is the language at column 3, line 3, following the structural formula denoted (I') incorrect or is it an inaccurate description of the subject matter? Applicants fail to specifically delineate when and how an error arose as a result of compounds being deleted from the scope of the claims

during prosecution of the parent. The reissue oath should state when and how the compounds of claims 3 to 8 were found to possess unobviously superior activity to DMDC. The reissue declaration also fails to specify in detail how new claims 9 and 10 overcome the errors wherein the inventors claimed more than they had a right to claim in the patent and less than they had a right to claim in the patent. With regard to claiming less than they had a right to claim in the patent, it is noted that applicants fail to specify when the error in prosecution concerning "claiming less than they had a right to claim in the patent" arose and when it was discovered. Applicants are requested to provide dates which reflect the determination of when an error arose and/or was discovered as accurately as possible.

Claims 1-10 are rejected as being based upon a defective reissue declaration under 35 U.S.C. § 251. See 37 C.F.R. § 1.175.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how

to make and or use the invention (i.e. failing to provide an enabling disclosure).

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974).

While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in the instant application in such details, including proportions and techniques where necessary, as to enable those persons skilled in the art to make and utilize the invention.

Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. The statute specifically requires that applicant provide an adequate written description which teaches how to make and use the invention claimed. The instant disclosure does not provide sufficient data to substantiate the anti-cancer activity, more specifically the antitumor activity, as well as antiviral activity of the class of compounds as broadly set forth. Markush claims must be provided with support in the disclosure. Markush claims are subject to rejection based upon the lack of supporting disclosure when the "working examples" fail to include written

description(s) which teach how to make and use Markush members embraced thereby in full, clear and exact terms, see Ex parte Haury (POBA 1948) 127 USPQ 52 and In re Fouche (CCPA 1971) 439 F2d 1237, 169 USPQ 429. There is presently not seen an adequate written description which teaches how to make and use compounds of this class as encompassed by the Markush groups delineated. Where the constitution (ability of the instantly claimed compounds encompassed by the Markush groups to act as antiviral and antitumor agents) and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula. A disclosure involving a new chemical compound or composition must teach persons skilled in the art how to make and use the compound. The instant specification fails to provide an adequate written description which would teach the skilled artisan in this field how to use the instantly claimed compounds as antiviral agents and also fails to teach the broad spectrum applicability of the compounds as anti-cancer agents specifically effective against tumors.

The objective truth of the broad anti-cancer applicability of the instantly claimed 2'-deoxy-2'-methylidine pyrimidine compounds as well as the applicability of the compounds claimed as anti-tumor agents and anti-viral agents is questioned in view of the state of this art at the time the invention was made, specifically since there are few agents recognized as successful

broad spectrum anti-cancer agents with broad spectrum anti-tumor activity and broad spectrum anti-viral activity.

The specification hints that the claimed compounds have therapeutic applications for the in vivo treatment of tumors in animals as evidenced by the oral and parenteral modes of administration contemplated. The invention as claimed is described as a compound which exhibits an anti-cancer effect, see column 5. The term "cancer" is defined as a neoplasm or cellular growth whose unique characteristic -loss of normal controls- results in unregulated cell growth, lack of differentiation, and ability to invade local tissues and potentially metastasize. Cancer includes inherited cancers encompassing not only tumors, but also leukemic conditions (malignant neoplasms of the blood-forming tissues) and lymphomic conditions (neoplasms arising in the reticuloendothelial and lymphatic systems). The instant specification is silent as to how the skilled artisan would treat leukemic and lymphomic conditions. Leukemic and lymphomic forms of cancer are not seen as adequately addressed in the instant specification and the data presently set forth in said specification is insufficient to correlate efficacy of the instantly claimed compounds to encompass the treatment of leukemias, lymphomas or tumors (i.e. cancer). The instant specification is deficient in establishing the antiviral efficacy of applicants' compounds. The disclosure is insufficient to support the allegation that the instantly claimed compounds are

"anti-cancer" compounds and the objective truth of such is doubted. The specification does not provide proof to the contrary. This art does not recognize correlating the efficacy of nucleoside compounds exhibiting activity against transplanted leukemia cells into three mice to the extrapolation of efficacy against transplanted and non-transplanted tumors, leukemias and lymphomas. This art also fails to recognize correlating the efficacy of nucleoside compounds exhibiting activity against transplanted leukemia cells into three mice to the extrapolation of efficacy against viruses.

As the instant disclosure relates to the treatment of tumors, it is noted that the art recognizes that tumors can develop in any tissue of an organ. Presently the instant specification makes no differentiation between the instant active ingredient's ability to treat inherited tumors or tumors caused by environmental factors (i.e. chemically induced tumors, transplanted tumors). In the absence of adequate demonstration of the broad spectrum efficacy of the instant compounds as anti-tumor agents, these prophetic statements are considered speculative and/or border on the incredible, and the claimed subject matter is not seen to be broadly efficacious against tumors. There are no known active agents with so broad a range of anti-tumor activity for the different types of tumors known as is alleged for the instant compounds and the objective truth of the efficacy of the instant compounds as broad spectrum anti-tumor

agents is doubted based on the contemporary knowledge in the art. It is noted that the instant specification advances little to substantiate the allegations that the instant compounds are anti-viral compounds. It is noted that there is not seen a written description which teaches how to use compounds which include a representative number of the members represented by the variables R_1, R_2, R_3 and R_4. Where the constitution (e.g. anti-cancer, anti-tumor or anti-viral activity) of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such constitution.

The instant specification invites the skilled artisan to experiment. The factors which must be considered in determining undue experimentation are set forth in Ex parte Forman 230 USPQ 546. The factors include 1) quantity of experimentation necessary, 2) the amount of guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the predictability of the art and the 7) breath of the claims.

With regard to factors one and two cited above, the quantity of experimentation needed to determine the specific identity and amounts of the active ingredients selected from among those encompassed by the instant Markush compound claims, the time table necessary to achieve efficacious administration against tumors or viruses, as well as the specific identity of the

specific tumors and viruses for which the instant applicability of the compounds is alleged would be incredibly voluminous and require undue experimentation. The specification does not provide adequate guidance in the written description for the treatment of the plethora of known tumors or viruses. There has not been advanced an adequate written description which embraces the arts mode for formulating successful cancer therapy, wherein the therapy must be directed primarily to the tumor or metastases, whether clinically apparent or microscopic. Where applicants allege that the instant compounds are anti-cancer agents, it is noted that there are no teachings which would direct the skilled artisan in methodologies which include local and regional therapy, surgery or radiotherapy, all of which are usually integrated with systemic therapy (chemotherapy).

With regard to factors four, five and six, it is noted that there is a great deal of unpredictability in cancer treatment (including the treatment of neoplasms, lymphomas and leukemias) and specifically in the treatment of tumors, even though it is known in the art that some neoplasms and tumors are responsive to chemotherapy. It is also noted that there is a great deal of unpredictability in antiviral treatment (including retroviruses and HBV). It would appear that applicants would like the skilled artisan in this field to equate a compound's efficacy inhibiting the instant transplanted L-1210 ($1x10^5$) leukemia cells with proof of anti-cancer, or more specifically, broad anti-tumor activity

or antiviral efficacy for said compounds. This test is an art recognized screen for potential therapeutic agents for further investigation for efficacy. This art does not equate positive results in screening tests such as the efficacy of the instantly claimed compounds as shown in the Pharmacological Experiment example advanced in the instant specification with broad spectrum anti-tumor efficacy against non-tumor forms of "cancer" or viruses. The instant specification provides no guidance for treating cancers such as non-transplanted Leukemias, Lymphomas Transplanted or Non-transplanted tumors or Viruses. It is noted that applicants have submitted the Miyashita et al. article (Nucleosides and Nucleotides, V. 11(2-4), pages 495-513, which shows that the attachment of different acyl groups to an anti-tumor core 2'-deoxy-2'-methylidene pyrimidine nucleoside compound may result a broad range of activity against transplanted tumors.

With regard to factors three and seven, it is noted that the working examples are limited to efficacy of the compound of Example 3 against cells of L-1210 leukemia cells. Such is not seen as sufficient to support the breath of the claims, wherein the scope of the claims encompasses compounds which encompass far more than singular example advanced in the Pharmacological Experiment. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves., see In re Gardner et al. 166 USPQ 138 (CCPA

1970). In the instant case, applicants have failed to teach the skilled artisan in this field how to treat or inhibit non-transplanted tumors or viruses.

The Declaration submitted October 4, 1993 by Akihiro Fujii has been carefully reviewed and is not convincing of the anti-cancer, anti-tumor or antiviral efficacy of the instantly claimed compounds. Declarations presented to show that the disclosure of an application is sufficient to one skilled in the art are not acceptable to establish facts which the specification itself should recite: In re Smyth, 1951 C.D.587, 62 USPQ 297, 31 CCPA 1248.

Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to whose telephone number is (703) 308-4624.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

James O. Wilson

JOHN W. ROLLINS
PRIMARY EXAMINER
ART UNIT 183